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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/866,034	05/25/2001	David Botstein	P2930R1C1	4767

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KNOBBE, MARTENS, OLSON AND BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/866,034	BOTSTEIN ET AL.	
	Examin r	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27 and 32-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27, 27, 32-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Office Action:

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/24/2003 has been entered.

Claims 27, 28 and 32-35 are pending and under consideration.

Objections and Rejections under 35 U.S.C. §101 and §112:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 27, 28 and 32-35 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility.

Note that this rejection has been recast. In reviewing the record, the Examiner has determined that prosecution has strayed from the salient issues, and issues first raised in the first action on the merits no longer apply, due to amendment of the claims. Accordingly, the rejection is set forth anew in order to focus the issues.

The claims are directed to isolated polypeptides comprising SEQ ID NO: 2. Dependent claims are directed to chimeric proteins comprising the aforementioned polypeptides. The specification contains numerous asserted utilities at pages 81-98 including use to identify molecules that bind to PRO (including agonists and antagonists), as molecular weight markers, therapeutic agents, and for the production of antibodies. The utilities that pertain solely to nucleic acids (e.g. hybridization, chromosome and gene mapping, anti-sense) would not convey

to the encoded protein. With respect to the remaining utilities, none of these asserted utilities is specific for the disclosed PRO1800 protein, as each of the aforementioned utilities could be asserted for any naturally occurring protein, and further, as none of the asserted utilities requires any feature or activity that is specific to the disclosed PRO1800.

The specification teaches that PRO1800 has (unspecified) homology to Hep27, which Hep27 is a member of the short chain alcohol dehydrogenase protein family (page 2). At page 70, the specification states that PRO1800 is a "newly identified Hep27 homolog, and possesses activity typical of that protein", however no activity is known or disclosed for Hep27. The structure of the putative PRO1800 peptide is discussed at page 103 of the specification. There is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO1800. Without any information as to the specific properties of PRO1800, the mere identification of such as belonging to the "short chain alcohol dehydrogenase protein family" is not sufficient to impart any particular utility to the claimed polypeptides.

At pages 116-117, it is disclosed that nucleic acids encoding PRO1800 had a ΔCt value of at least 1.0 for a number of primary lung and colon tumors, but not for all but one of the tested colon or lung tumor cell lines. Even *if* the data demonstrated a slight increase in copy number of PRO1800 nucleic acids in primary tumors, such would not be indicative of a use of the encoded polypeptide as a diagnostic agent. Cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, 2000, Curr. Opin. Oncol. 12:82-88). A slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. The preliminary data were not supported by analysis of mRNA or protein expression, for example. Also, the literature reports that it does not necessarily follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression, such that the claimed polypeptides would be useful for diagnosis of cancer or as a drug target. For example, Pennica et al. (1998, PNAS USA 95:14717-14722) disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its

> mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors." Therefore, data pertaining to PRO1800 nucleic acids do not necessarily indicate anything significant regarding the claimed PRO1800 polypeptides. Thus, the data do not support the implicit assertion that PRO1800 can be used as a cancer diagnostic. Significant further research would have been required of the skilled artisan to determine whether PRO1800 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic, and thus the implicitly asserted utility is not substantial.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-34 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Priority Determination:

As the claimed subject matter is found to lack utility and enablement under 35 U.S.C. § §101 and 112, first paragraph, respectively, the effective priority date for this application is the instant filing date, 5/25/01.

Rejections over Prior Art:

A search of the protein sequence databases revealed the following prior art:

Locus	Date	Author	Identity to SEQ ID NO:2
Q9BTZ2	2/01	Strausberg	100%
Q9H3N5	6/00	Furukawa	100%, residues 19-278
O95162	5/1/99	Fransen	99.2%, residues 19-278
AF044127	5/27/99	Fransen	99.3% (1 conservative sub.)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 22-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Fransen et al. locus O95162. As summarized above, Fransen et al. disclose locus O95162, which has 99.2% identity to SEQ ID NO: 2 lacking its signal peptide, i.e. residues 19-278 of SEQ ID NO: 2.

Claims 22-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Fransen et al. locus AF044127. As summarized above, Fransen et al. disclose locus AF044127, which has 99.3% identity to the entirety of SEQ ID NO: 2 .

Claims 22-29 and 32 are rejected under 35 U.S.C. 102(a) as being anticipated by Strausberg, locus Z9BTZ2, or Furukawa et al., locus Q9H3N5. As summarized above, the two proteins are 100% identical to the entirety of SEQ ID NO:2, and 100% of residues 19-278 of SEQ ID NO: 2, which is the polypeptide lacking its signal sequence.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-29 and 32 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Fransen et al. locus O95162 or locus AF044127.

As discussed above, Fransen et al. disclose an isolated two polypeptides having over 99% amino acid sequence identity to the amino acid sequence of the polypeptide shown in SEQ ID NO: 2. The single difference in amino acid sequence between the polypeptide of SEQ ID NO: 2 recited in the instant claims and the polypeptides of Fransen et al. occurs at position 126. Specifically, the amino acid at position 126 in SEQ ID NO: 2 of the instant application is isoleucine, whereas the corresponding amino acid of Fransen et al. is leucine. This is a conservative amino acid substitution.

The courts have long recognized that sequencing errors can occur (*Ex parte Maizel*; 27 USPQ2d 1662, BPAI 1992, see especially pp. 1663 and 1666). The instant specification also recognizes that the sequences disclosed in their sequence listings and Figures may not be exact. At page 70 of the instant specification, it is stated that:

> "For the PRO polypeptides and encoding nucleic acids described herein, Applicants have identified what is believed to be the reading frame best identifiable **with the sequence information available at the time.**" (emphasis added)

Therefore, it is reasonable to expect that the single amino acid difference at position 126 of SEQ ID NO: 2 of the instant application and Fransen et al. may be the result of a sequencing error, and that the actual clones of the instant application and Fransen et al., in fact, have identical sequences.

The examiner is unable to determine whether the prior art disclosures actually possesses the characteristic of the sequence of SEQ ID NO: 2. Under such circumstances, where the product seems to be identical, then the burden shifts to applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Note the case law of *In re Best* 195 USPQ 430, 433 (CCPA 1977).

Claims 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Fransen et al. locus O95162 or locus AF044127, or Strausberg, locus Z9BTZ2, or Furukawa et al., locus Q9H3N5, any one in view of Hopp et al., U.S. Patent Number 5,011,912.

The teachings of the four primary references are cited above. All of the protein sequences are clearly identified as being from nucleic acid sequence, indicating that the nucleic acids encoding the proteins had been cloned. None of the primary references teaches expression of the protein as a fusion protein comprising an epitope tag or Fc region.

Hopp et al. teach the use of an amino acid sequence, "DYKDDDDK", which is disclosed as being immunogenic, for use in producing fusion proteins which can then be easily purified. See, for example, column 2, lines 45-57. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the protein of any one of the primary references by producing such as a fusion protein comprising the flag amino acid sequence of Hopp et al., for the purpose of being able to easily purify the proteins of the primary references. The motivation and expectation of success are both taught by Hopp et al. who teach the flag peptide/monoclonal antibody purification system as being generally useful for such.

Conclusion:

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M. ***Effective 1/21/2004, Dr. Spector's telephone number is 571-272-0893.***

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz. ***Effective 1/21/2004, Dr. Kunz' telephone number is 571-272-0887.***

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Lorraine Spector, Ph.D.
Primary Examiner

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2/6/04